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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/484,121	01/13/2000	Ralf Reiner Schumann	103888-307-NP	9305

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/484,121	SCHUMANN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 34-41 are pending.

Applicants' amendment filed October 16, 2003 is acknowledged. Applicants' response has been fully considered. Claims 12-18, 22, 23 and 28-33 have been cancelled, and new claims 34-41 have been added. Thus, claims 34-41 are examined.

Objection Withdrawn

Claim Objection

2. The previous rejection of claim 32 is withdrawn in view of applicants' cancellation of the claim in the amendment filed October 16, 2003.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 32 and 33, under 35 U.S.C. §112, first paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed October 16, 2003.

4. The previous rejection of claim 33, under 35 U.S.C. §112, second paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed October 16, 2003.

Claim Rejections - 35 USC § 102

5. The previous rejection of claims 28, 32 and 33, under 35 U.S.C. §102(b) as being anticipated by Scott *et al.* (WO 94/25476), is withdrawn in view of applicants' cancellation of the claim in the amendment filed October 16, 2003.

6. The previous rejection of claims 28 and 33, under 35 U.S.C. §102(b) as being anticipated by Heavner *et al.* (WO 95/08560), is withdrawn in view of applicants' cancellation of the claim in the amendment filed October 16, 2003.

Claim Rejections - 35 USC § 102&103

7. The previous rejection of claims 29-31, under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Scott *et al.* (WO 94/25476), is withdrawn in view of applicants' cancellation of the claim in the amendment filed October 16, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detoxifying bacterial lipopolysacchride (LPS) in mice comprising determining an effective amount of murine lipopolysacchride binding protein (mLBP, native or recombinant) and administering the effective amount of mLBP to mice to elevate the concentration of serum LBP to a certain level (e.g., about 7.5 μg/ml) to suppress the LPS-Induced release of cytokine in a LBP septicemia model, does not reasonably provide enablement for a method for detoxifying bacterial LPS in a patient with septicemia or preventing toxification of bacterial LPS (not even occurs at the first time) in a subject at risk of exposure to gram-negative or gram-positive bacteria comprising determining an effective amount of LBP and administering the effective amount of LBP to the patient to elevate the concentration of LBP to a

sufficient high level to suppress LPS-Induced release of cytokine, where the LBP administered, and the concentration of LBP in patient are not specified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 34-41 are directed to a method for detoxifying bacterial LPS in a patient with septicemia (claims 34-40) or preventing toxification of bacterial LPS in a subject at risk of exposure to gram-negative or gram-positive bacteria (claim 41) comprising determining an effective amount of LBP and administering the effective amount of LBP to the patient to elevate the concentration of LBP to a sufficient high level to suppress LPS-Induced release of cytokine. The specification, however, only discloses cursory conclusions (page 1, line 19-page 2, line 9) without data supporting the findings, which states that the instant invention is related to develop an agent for the treatment of septicemia, where the agent contains LBP from different species such as human, murine or rabbit, or recombinant LBP or its mutants. There are no indicia that the present application enables the full scope in view of the method of detoxifying bacterial LPS in a patient with septicemia or preventing toxification of bacterial LPS in a subject as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the LBP from different species, the LBP mutants, and the concentrations of LBP in patient to suppress LPS-Induced release of cytokine, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification indicates that the murine macrophage cell lines stimulated by bacterial LPS is LBP concentration dependent, where the production of TNF-α is LBP and serum dependent (Figs 1-3); administering murine LBP at high dosage (e.g., 100 μg/ml) to mice suppresses the production of TNF-α or IL-6, suppresses the liver damage induced by LPS, and reduces the lethality of animals in a LBP septicemia model, where the serum concentration of LBP in mice is about 7.5 μg/ml (Figs. 4-7). There are no other workings examples indicating the claimed method.

(3). The state of the prior art and relative skill of those in the art:

The related art, e.g., Schmann et al. (Science 249, 1429-1431 (1990)) indicates LBP potentiates the host response to LPS, eventually resulting in pathogenic states such as septic shock; Lamping et al. (J. Clin. Invest. 101, 2065-2071 (1998)) describes mLBP at high concentration detoxify LPS in vitro and in a mouse septicemia model; Dedrick et al., (U. S. Patent. 5,990,082) indicates human subjects suffering from disorders involving bacterial endotoxins exhibit substantially elevated circulating levels of LBP (50-100 mg/ml in serum), yet these high circulating levels of LBP do not appear to inhibit the advise effects of bacterial endotoxin in circulation, thus, the role of LBP in promoting or alleviating adverse effects of

endotoxin in circulation remains unclear (the references have been provided in Paper No.14, dated 6/18/01); regarding LBP from different species, it appears there are sequence variations among murine, rat rabbit and human LBPs (Su et al., I. Immunology 153, 743-752 (1994)), thus the activity of murine LBP might be different from the LBP from other species. Since the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identity and the amount of LBP administered, the concentration of LBP in patient produced, and the effect of LBP in suppressing release of cytokine to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for detoxifying bacterial LPS or preventing toxification of bacterial LPS in a subject comprising determining an effective amount of LBP and administering the effective amount of LBP to the patient to elevate the concentration of LBP to a sufficient high level to suppress LPS-Induced release of cytokine. However, the specification has not described the use of various LBPs in the treatment, nor has demonstrated the effects of various LBPs in suppressing release of cytokine in patients. Thus, the effects of LBP in detoxifying bacterial LPS is not predictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of detoxifying bacterial LPS or preventing toxification of bacterial LPS in a patient comprising determining an effective amount of LBP and administering the effective amount of LBP to the patient to suppress LPS-Induced release of cytokine. The specification indicates that the murine macrophage cell lines stimulated by

bacterial LPS is LBP concentration dependent, where the production of TNF-α is LBP and serum dependent (Figs 1-3); and administering murine LBP at high dosage (e.g., 100 μg/ml) to mice suppresses the production of TNF-α or IL-6, suppresses the liver damage induced by LPS, and reduces the lethality of animals in a LBP septicemia model, where the serum concentration of LBP in mice is about 7.5 μg/ml (Figs. 4-7). However, the specification does not identify any mutants and hybrid proteins of LBP, nor discloses how to obtain these mutants and hybrid proteins of LBP, and how to use these proteins in detoxifying bacterial lipopolysaccharide in a patient with septicemia. Moreover, the specification does not provide any specific guidance such as the amounts of various LBPs administered to produce sufficient concentration of LBP in serum to suppress the release of a cytokine, nor describes how to prevent the toxification of bacterial LBS in a patient at risk of exposure to bacteria, e.g., if the disease does not occur, how to monitor it. There is no data indicating the effects of various LBPs other than mLBP in suppressing cytokine release and detoxifying LPS in a mouse model. Since the specification does not provide sufficient teachings, it is necessary to have additional guidance on the use of various LBPs in patients, and to carry out further experimentation to assess the effect of various LBPs in the treatment of LPS toxification in vivo.

(6). Nature of the Invention

The scope of the claims encompass a method of detoxifying bacterial LPS or preventing toxification of bacterial LPS in a patient by administering LBP, but the specification only demonstrates administration of a specific amount of mLBP in a mouse model, it does not demonstrate the use and the effect of various LBPs in detoxifying bacterial LPS or preventing

toxification of bacterial LPS. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods, the effects of various LBP are unpredictable, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of various LBPs in detoxifying bacterial LPS in a patient with septicemia.

9. Claims 37-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 37-40 are directed to a method for detoxifying bacterial lipopolysaccharide in a patient with septicemia comprising administering a LBP having increased binding affinity such as a LBP mutant and hybridization of LBP (claim 37), and the concentration of LBP in the patient is elevated to at least 4, 10 or 20 μg/ml, respectively (claims 38-40). The specification indicates that administering murine LBP at high dosage (e.g., 100 μg/ml) to mice suppresses the production of TNF-α, suppresses the liver damage induced by LPS and reduces the lethality of animals in a LBP septicemia model (Figs. 4-7), and LBP mutants are used as therapeutic agents for treatment of septicemia (page 2, lines 7-9), as well as the serum concentration of LBP in mice is about 7.5 μg/ml (Fig. 4). However, the specification does not identify any mutants and hybrid proteins of LBP nor discloses how to obtain these mutants and hybrid proteins of LBP, and how to use these proteins in detoxifying bacterial lipopolysaccharide in a patient with septicemia.

There is no structural or functional identification of the mutants or hybrid proteins of LBP. Moreover, the specification has not demonstrated the administration of LBP can elevate the concentration of serum LBP more than 10 or 20 μg/ml in patient (Fig. 4). Without guidance on structure to function/activity of the mutants or hybrid proteins of LBP, as well as teachings regarding the concentration of serum LBP, one skilled in the art would not know which region of the protein is essential for function/activity, how to identify a functional peptide, and what amount of LBP is administered to elevate the serum LBP more than 10 μg/ml. The lack of a structure to function/activity relationship of the protein and the lack of representative species for the mutants or hybrid proteins of LBP, as well as the lack of teaching regarding the concentration of serum LBP as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 34-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 34-41 are indefinite because the claim lacks an essential step in the method of detoxifying or preventing toxification of bacterial lipopolysaccharide in a patient. The omitted step is the outcome of the process. Claims 34 and 41 are also indefinite as to how to determine the effective amount of lipopolysaccharide binding protein (LBP) needed for detoxifying

bacterial lipopolysaccharide or for preventing toxification of bacterial lipopolysaccharide, e.g., whether the determining step is carried out in vitro or in vivo, and what is used as a marker for the determination. Claims 34 and 41 are also indefinite because of the use of the term "elevates the concentration of lipopolysaccharide binding protein ....to a sufficiently high level to suppress lipopolysaccharide-induced release of cytokine", it is not clear what is the concentration of LBP as to "a sufficiently high level to suppress release of cytokine", and how much cytokine is suppressed. Claims 35-40 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

12. Claim 37 is indefinite because of the use of the term "the binding affinity of said lipopolysaccharide binding protein" or "by means of mutations or hybridization". The term cited renders the claim indefinite, it is unclear what is the target for the binding affinity of LBP; where is the mutation in the sequence of LBP, and what mutation is intended; what is hybridization of LBP, and how the hybridization of LBP enhances the suppression of lipopolysaccharide-induced release of cytokine.

Conclusion

13. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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December 18, 2003

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
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